REMARKS

The present invention relates to the use of marrow stromal cells to enhance hematopoiesis in a mammal. Claims 1-16 are currently pending and under consideration in the present application following entry of the present Amendment. Claims 1, 5, 9, 13-16 have been amended herein.

Supplemental Declaration

Applicants respectfully submit that an executed declaration was filed November 20, 2001, in response to the Notice to File Missing Parts. This declaration was executed by all three inventors, Darwin J. Prockop; Russell G. Reiss; and John Langell. While not necessarily agreeing with the Examiner's assertion that the executed declaration filed November 20, 2001 is defective because the Applicants did not sign the declaration, Applicants submit herewith an executed substitute declaration. Further, this executed substitute declaration filed herewith also correctly identifies the present application by application number and filing date. Upon entry of the present Amendment and the executed supplemental declaration, Applicants respectfully contend that the executed supplemental declaration fully complies with 37 CFR § 1.67(a).

Supplemental Information Disclosure Statement

Applicants herewith submit a Supplemental Information Disclosure Statement and the attached Information Disclosure Citation Form PTO-1449. It is requested that the enclosed references listed on the Form PTO-1449 be considered by the Examiner and be made of record.

Amendment to the Application to claim priority under 35 U.S.C. § 119(e)

Page 1 of the specification has been amended to add priority claim to the prior International Application No. PCT/US99/25134, filed October 26, 1999 and to U.S. Provisional Application No. 60/105,671, filed October 26, 1998.

Applicants respectfully submit that the priority was correctly claimed on the transmittal form filed with the present application on April 20, 2001. Further, Applicants respectfully point out to the Examiner that the Filing Receipt indicates that the USPTO recognized that the present application is a continuation of International Application No. PCT/US99/25134, filed October 26, 1999, which claims benefit to U.S. Provisional Patent

Application 60/105,671, filed October 26, 1998. Thus the amendment to the specification to add priority claim is not new, as the priority claim was properly claimed on the Application Transmittal Form filed with the present application on April 20, 2001.

Rejection of Claims 1-16 Under 35 U.S.C. § 112, second paragraph

Claims 1-16 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner contends that claims 1-16 are indefinite because it is unknown what else is "otherwise identical" between the allogenic donor and the recipient. While not necessarily agreeing with the Examiner that the claims are indefinite for reciting such term, but rather in a good faith effort to expedite the prosecution of this application, Applicants have deleted "but otherwise identical" from claims 1, 5, 9, 13-16. Applicants respectfully contend that the rejection of claims 1-16 based on the recitation of "otherwise identical" is rendered moot in view of the amendments to the claims and should be withdrawn.

Rejection of claims 1, 2, 4-6, 8-10 and 12-16 pursuant to 35 U.S.C. § 102(b)

Claims 1, 2, 4-6, 8-10 and 12-16 stand rejected under U.S.C. § 102(b) as being anticipated by Anklesaria et al. (1987, Proc. Natl. Acad. Sci., USA 84:7681-85). Specifically, the Examiner opines that Anklesaria et al. teaches engraftment of a clonal bone marrow stromal cell line *in vivo* to stimulate hematopoetic recovery from total body irradiation, thereby anticipating the present invention. Applicants respectfully traverse this rejection for the following reasons.

It is well settled that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP §2131 (quoting *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). "The identical invention must be shown in as complete detail as is contained in the . . . claim." *Id.* (quoting *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Therefore, Anklesaria et al. must describe each and every element of claims 1, 2, 4-6, 8-10 and 12-16, in order to anticipate these claims under Section 102(b), and this reference does not.

Applicants respectfully contend that Anklesaria et al. does not anticipate the

present invention because the reference does not teach an isolated marrow stromal cell as recited in the amended claims herein and described in the as-filed specification. That is, we are of the opinion that Anklesaria et al. teaches a stable clonal cell line (GB1/6) which was established from the adherent layer of long-term marrow cultures from B6Cast mice. One skilled in the art would appreciate that the long-term marrow stromal cells of Anklesaria et al. are transformed or immortalized and have obtained characteristics of a malignant cell which enables the so called long-term marrow cells to be cultured indefinitely. Applicants assert that one skilled in the art would appreciate based upon the disclosure of the instant application, that the isolated marrow stromal cells of the present invention are short-term cultures, wherein the cells are administered to an irradiated mammal before the cells are transformed or immortalized into a stable cell line. That is, one skilled in the art would appreciate based upon the disclosure of the present application that the isolated marrow stromal cells of the present invention when cultured, are cultured in a manner in which one skilled in the art would recognize that the cells of the present invention are primary cultured marrow stromal cells. For example on page 9 of the specification, it is disclosed that the marrow stromal cells are administered to a mammal upon isolation or following a period of in vitro culturing. Further, the specification beginning on page 15 discloses that the isolated marrow stromal cells are cultured in vitro prior to transplantation into a mammal. The specification does not discuss the isolated morrow cells to be a stable cell line, and one skilled in the art would not consider the cells of the present invention base on the disclosure of the instant application to be a stable cell line.

Further, Applicants contend that the primary cultured marrow stromal cells of the present invention are not anticipated by the cells of Anklesaria et al. because the cells of the present invention are not selected for neomycin resistance. That is, Anklesaria et al. teaches a stable clonal cell line (GB1/6) which was established from the adherent layer of long-term marrow cultures from B6Cast mice and made resistant to neomycin by retroviral gene transfer. As described in Anklesaria et al., the stable clonal cell line was subcloned from a clone containing the neomycin gene and was selected for in G418. Anklesaria et al. does not teach an isolated or primary culture marrow stromal cell as described in the as-filed specification. Nowhere does the as-filed specification of the instant application discloses neomycin and having the isolated marrow stromal cells selected and made resistant to neomycin. Therefore, one skilled in the art would appreciate that an embodiment of the present invention is the

administration of the isolated cultured marrow stromal cells to an irradiated mammal without having the cells be selected for neomycin resistance. Applicants respectfully contend that Anklesaria et al. does not teach an isolated marrow stromal cell that has not been selected for neomycin, and as such, cannot anticipate the present invention. Accordingly, Applicants request that the rejection of claims 1, 2, 4-6, 8-10 and 12-16 under U.S.C. § 102(b) be reconsidered and withdrawn upon entry of the present Amendment for the reasons set forth elsewhere herein.

Rejection of Claims 3, 7 and 11 pursuant to 35 U.S.C. §103(a)

The Examiner has rejected claims 3, 7 and 11 pursuant to 35 U.S.C. § 103(a), as being obvious over Anklesaria et al., and in further view of Palsson et al. (U.S. Patent No. 5,635,386). Specifically, the Examiner contends that Palsson et al. teaches the use of human hematopoietic stem cells and their cultures that "afford improved methods for bone marrow transplantation," and the combination of the teachings of Anklesaria et al. with Palsson et al. would arrive at the present invention. Applicants respectfully traverse this rejection for the following reasons.

The three-prong test must be met for a reference or a combination of references to establish a *prima facie* case of obviousness, and this criteria has not been satisfied in the instant matter. The MPEP states, in relevant part:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. MPEP § 2142.

None of these criteria have been met here.

The present invention encompasses a method of rescuing a mammal from a lethal dose of total body irradiation, said method comprising administering isolated marrow stromal cells from an allogenic donor mammal to an irradiated mammal, thereby rescuing said mammal from a lethal dose of total body irradiation. Neither Anklesaria et al. nor Palsson et al. suggest to or motivate the skilled artisan to arrive at the present invention. That is, neither Anklesaria et al. nor Palsson et al. suggest that the administration of a donor isolated marrow stromal cell, as described in the present application, would rescue a mammal from a lethal dose of total body

irradiation.

Applicants argue that Anklesaria et al. offers no suggestion or motivation to modify the reference or to combine reference teachings to arrive at the present invention. Further, Anklesaria et al. does not offer the skilled artisan a reasonable expectation of success and does not teach or suggest all of the claim limitations.

As discussed elsewhere herein, Anklesaria et al. teaches a stable clonal cell line (GB1/6) which was established from the adherent layer of long-term marrow cultures from B6Cast mice and made resistant to neomycin. Thus, Anklesaria et al. does not teach the use of Applicant's cells. The teachings of Palsson et al. does not correct the deficiency of Anklesaria et al. That is, Palsson et al. teaches the use of human hematopoietic stem cells and their cultures that "afford improved methods for bone marrow transplant." Palsson et al. does not mention the use of isolated marrow stromal cells as described in the as-filed specification to be administered to a mammal for rescuing a mammal from total body irradiation.

As an initial matter, Palsson et al. teaches the culturing of hematopoietic stem cells in the presence of marrow stromal cells in vitro to enhance the production of a hematopoietic cell. The co-culturing of the hematopoietic stem cells with the marrow stromal cells helps in the maturation of the hematopoietic stem cells into cells of the hematopoietic lineage. That is, Palsson et al. teaches a cell culture media comprising hematopoietic stem cells and marrow stromal cells, wherein the hematopoietic stem cells cell are in contact with the marrow stromal cells in order for the hematopoietic stem cells to receive any benefit from the morrow stromal cells. However, the present invention teaches that the hematopoietic reconstitution is an endogenous phenomenon without the requirement of having the hematopoietic stem cells be in contact with the marrow stromal cells. That is, on page 21 of the as-filed specification, it is disclosed that no positive staining of the infused marrow stromal cells was detected in recipient mammals following infusion. Thus, one skilled in the art when armed with the teachings of the specification would be able to appreciate that the infused marrow stromal cells disappear following a short time after the administration of the marrow stromal cell to a mammal, and that a major effect of the infused marrow stromal cells is the production of cytokines and other growth factors for the benefit of the endogenous hematopoietic stem cells without having the infused marrow stromal cells and the endogenous hematopoietic stem cells be in direct contact with each other. In fact, Palsson et al. teaches away from the present invention

because Palsson et al. teaches the co-culturing of both hematopoietic stem cells and marrow stromal cells, and that the two cells are required to contact one another in order for the maturation of the hematopoietic stem cell.

Further, Applicants contend that Palsson et al. does not disclose that marrow stromal cells, when infused in vivo, would restore the endogenous hematopoietic system. At best, Palsson et al. teaches ex vivo technology wherein hematopoietic cells are produced by the co-culture system in vitro as discussed elsewhere herein, and that the hematopoietic cells are used in bone marrow transplant in a patient that has depleted T or B cells. Therefore, Palsson et al. does not teach the in vivo infusion of a marrow stromal cell to a mammal to enhance hematopoiesis. Palsson et al., even in view of Anklesaria et al., fails to offer a suggestion or motivation to modify the reference to arrive at the instant invention.

The second criteria for establishing a *prima facie* case of obviousness is that there must be a reasonable expectation of success. Anklesaria et al. describes the use of a stable clonal stromal cell line, which was made resistant to neomycin, in the stimulation of hematopoietic recovery from total body irradiation. Thus, from the disclosure set forth in Anklesaria et al., the skilled artisan would not have any reason to expect that the isolated marrow stromal cell of the present invention, which is not a stable cell line and has not been selected for neomycin resistance, would rescue a mammal from a lethal dose of total body irradiation. From this, one skilled in the art would have no reason to expect success in rescuing a mammal from a lethal dose of body irradiation by administrating the cells of the present invention to a mammal, and therefore, Anklesaria et al. fails to render the present invention obvious.

Palsson et al., when combined with the teachings of Anklesaria et al. do not generate a reasonable expectation of success in rescuing a mammal from total body irradiation by administering a mammal with isolated marrow stromal cells. That is because Palsson et al. teaches hematopoietic stem cells and Anklesaria et al. teaches a cell line made resistant to neomycin, together one would have no reasonable expectation of success in combining the teaching of the two references to arrive at a culture of primary marrow stromal cell being able to rescue a mammal from a lethal dose of total body irradiation.

The third prong in establishing a *prima facie* case of obviousness requires the prior art reference or references to teach or suggest all of the claim limitations. As discussed elsewhere herein, Anklesaria et al. does not teach isolated marrow stromal cells, as defined in the

specification. Further, the cells described in Anklesaria et al. are not primary cultures. Therefore, Anklesaria et al. does not teach or suggest all aspects of the claims. In addition, the teachings of Palsson et al. as discussed elsewhere herein are unable to correct this defect in the teachings of Anklesaria et al., and therefore, Anklesaria et al., in view of Palsson et al., cannot render the present invention obvious. Accordingly, Applicants respectfully request reconsideration and withdrawal of the Examiner's rejection pursuant to 35 U.S.C. §103(a).

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has been overcome or is now inapplicable, and that claims 1-16 are now in condition for allowance. Reconsideration and allowance of these claims is respectfully requested at the earliest possible date.

Respectfully submitted,

DARWIN J. PROCKOP *ET AL.*

February 6, 2004
(Date)

By: Kathryn Doyle

KATHRYN DOYLE
Registration No. 36,317
MORGAN, LEWIS & BOCKIUS, LLP
1701 Market Street
Philadelphia, PA 19103-2921
Telephone: (215) 963-5000
Direct Dial: (215) 963-4723
Facsimile: (877) 432-5001
E-Mail: kdoyle@morganlewis.com
Attorney for Applicants

KD/QDN dlp
enclosures: Substitute Declaration
Information Disclosure Statement and Form PTO-1449
Petition for one month extension of time